SJS SRIWIJAYA JOURNAL OF SURGERY

**Sriwijaya Journal of Surgery Volume 4, Issue 1, Page No: 261 - 273**
**Available online: www.sriwijayasurgery.com**
**SJS 4(1): 261 - 273**

# Platelet/Lymphocyte Ratio Accuracy as Predictor of Neo-Adjuvant Chemotherapy Response in Locally Advanced Breast Cancer at Dr. Mohammad Hoesin General Hospital Palembang

Abdur Rahman[1], Mulawan Umar[2*], Erial Bahar[3]

[1]Department of Surgery Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia
[2]Oncology Unit, Surgery Department of Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia
[3]Department of Anatomy, Faculty of Medicine, Universitas Sriwijaya, Palembang, Indonesia
*Corresponding Author Email: mulawanumar@yahoo.com

## Abstract

**Background:** Platelet/lymphocyte ratio (PLR) is considered as predictor for chemotherapy response in locally advanced breast cancer undergoing neo-adjuvant chemotherapy. This study aims to evaluate the relationship between the platelet/lymphocyte ratio and neo-adjuvant chemotherapy response in patients with locally advanced breast cancer at Dr. Mohammad Hoesin General Hospital Palembang.

**Methods:** This study is a prognostic test of the platelet/lymphocyte ratio accuracy to predict the response of neo-adjuvant chemotherapy in patients with locally advanced breast cancer. The study included 113 subjects.

**Results:** From 113 patients, the PLR cut off point value was 206.83 with an under curve area (AUC) of 91.8%. The results of the PLR prognostic test were sensitivity of 98%, specificity of 87%, Positive Predictive Value of 95%, Negative Predictive Value of 93%, and 95% of accuracy. There was a significant relationship between PLR and chemotherapy response in patients with locally advanced breast cancer (p = 0.000).

**Conclusion:** There was a significant relationship between PLR on chemotherapy response. PLR can be used as a predictor of neo-adjuvant chemotherapy response with a good degree of accuracy.

**Keywords**: platelet/lymphocyte ratio, neo-adjuvant chemotherapy, breast cancer

## 1. Introduction

Breast cancer is a malignancy of the breast tissue that originates from the ducts or lobules of the breast, and is the most common type of malignancy in women in developed countries and second after cervical cancer in developing countries.[1,2,3] According to International Agency for Research on Cancer (IARC) WHO in the 2018 GLOBOCAN survey, breast cancer is the second leading cause of morbidity and mortality worldwide after lung cancer, with 2,088,849 cases (11.6%) and 626,679 deaths (6,6%) of all cancer-related cases.[4] In 2012, the incidence and mortality rate due to breast carcinoma in Indonesia were the highest with 48,998 new cases and 19,750 cancer related death.[5]

In developed countries where there are mass screening programs and good community education about cancer, more than 50% of breast cancer patients come at early stage, 10-20 patients out of 100,000 populations per year come with DCIS (Ductal Carcinoma In Situ) and some come with non-palpable breast cancer.[1] In Indonesia, breast cancer screening is still individual and sporadic, thus early detection program is considered inefficient and ineffective. More than 80% of cases were found at advanced stage.[3] Locally Advanced Breast Cancer (LABC) is currently the most common type of cancer (50-60%) found at outpatient clinics or hospitals in Indonesia.[6]

Neo-adjuvant chemotherapy is a therapeutic option in patients with locally advanced breast cancer. Neo-adjuvant chemotherapy is a type of chemotherapy that is given before primary therapy. Neo-adjuvant chemotherapy aims to reduce tumor size (tumor shrinkage) and control micrometastasis.[2] With neo-adjuvant chemotherapy, tumor removal is expected to improve, so that breast-conserving surgery can be performed. In the case of locally advanced breast cancer, neo-adjuvant chemotherapy is given in 3-4 cycles before locoregional therapy and can be continued after.[13] The response to neo-adjuvant chemotherapy can be assessed by comparing the mass size before and after chemotherapy. The therapeutic response is assessed with RECIST into the following classifications: complete, partial, stable and progressive.[7]

In recent years, platelet/lymphocyte ratio (PLR) has been proposed as an indicator for evaluating the systemic inflammatory response in patients with cancer and has shown utility as prognosis predictor in locally advanced breast cancer patients undergoing neo-adjuvant chemotherapy.[8]

Asano et al, reported that breast cancer patients with a low PLR had a better pathologic complete response to neo-adjuvant chemotherapy than patients with a high PLR. Thus it is suggested that PLR

could work as a predictor for neo-adjuvant chemotherapy response in patients with breast cancer.[8] Lopez et al, reported that breast cancer patients with a low platelet/lymphocyte ratio (PLR <150) who underwent neo-adjuvant chemotherapy showed a better pathologic complete response.[9] This is in line with the study of Xu et al, which stated that patients with a platelet/lymphocyte ratio low (PLR <151,27) had better response to neo-adjuvant chemotherapy.[10]

Based on the background above, through this study we wanted to investigate the role of PLR as predictor of chemotherapy response in locally advanced breast cancer at Dr. Mohammad Hoesin General Hospital Palembang.

## 2. Methods

This study is a prognostic test of the accuracy of the PLR to predict the response of neo-adjuvant chemotherapy in patients with locally advanced breast cancer.

The subjects of this study were patients with locally advanced breast cancer who received neo-adjuvant chemotherapy at Dr. Muhammad Hoesin Palembang General Hospital who met the inclusion criteria.

The inclusion criteria were patients with locally advanced breast cancer who were diagnosed based on the criteria of the American Joint Committee of Cancer and received adjuvant chemotherapy with Karnofsky index ≥ 50. The exclusion criteria were patients who had undergone previous chemotherapy and were immunocompromised.

There were 113 subjects in this study. The independent variables were the immunohistochemistry subtypes and the platelet/lymphocyte ratio. The dependent variable was the adjuvant chemotherapy response. The sociodemographic characteristics were age, age at menarche, history of hormonal contraception usage, age at first pregnancy, family history of breast cancer.

The data are presented in distribution and narrative tables. The receiver operating characteristics (ROC) curve statistical test was performed using the MedCalc 2000 software to determine the PLR cut off point value in predicting chemotherapy response. Chi square test to evaluate the sociodemographic relationship to the PLR value, and to evaluate the relationship between the PLR value and the chemotherapy response.

## 3. Results

### Sociodemographic characteristics distribution

There were 113 subjects who participated in the study. The average age was 47 years old, with the youngest was 27 years old and the oldest was 68 years old. There were 89 subjects aged above 40 years old (78.8%). There were 84 subjects (74.3%) age at menarche were at under 15 years old. There were 55 subjects (48.7%) who had their first pregnancy at under 30 years old. As many as 51 subjects (45.1%) had menopause at the age above 45 years old. There were 102 subjects (90.3%) with no family history of cancer. There were 86 subjects (76.1%) who used contraception. There were 90 subjects (79.6%) with childbirth history of more than one time. As many as 78 subjects (69%) had Luminal B subtype breast cancer. The results of the study are presented in table 1.

**Table 1.** Sociodemographic characteristics distribution

| Sociodemographic characteristics | Total (n) | Percentage (%) | P value |
|---|---|---|---|
| **Age** | | | |
| ≤ 40 years old | 24 | 21.2 | 0.475 |
| > 40 years old | 89 | 78.8 | |
| **Age at menarche** | | | |
| ≤ 15 years old | 84 | 74.3 | 0.733 |
| > 15 years old | 29 | 25.7 | |
| **Age at first pregnancy** | | | |
| Never been pregnant | 22 | 19.5 | |
| > 30 years old | 36 | 31.9 | 0.223 |
| ≤ 30 years old | 55 | 48.7 | |
| **Age at menopause** | | | |
| Not yet menopause | 33 | 29.2 | |
| ≤ 45 years old | 29 | 25.7 | 0.333 |
| > 45 years old | 51 | 45.1 | |
| **Family history of breast cancer** | | | |
| Yes | 11 | 9.7 | 0.438 |
| No | 102 | 90.3 | |
| **History of hormonal contraception usage** | | | |
| Yes | 86 | 76.1 | 0.113 |
| No | 27 | 23.9 | |
| **History of childbirth** | | | |
| 0 | 23 | 20.4 | 0.100 |
| ≥1 time | 90 | 79.6 | |
| **Subtype** | | | |
| Luminal A | 22 | 19.5 | |
| Luminal B | 78 | 69.0 | 0.405 |
| Triple negative | 10 | 8.8 | |
| HER2 Over | 3 | 2.7 | |

**Distribution of chemotherapy response in locally advanced stage breast cancer patients**

The distribution analysis results showed that 83 of the 113 subjects (73.5%) had good chemotherapy response. The research results are presented in table 2.

**Table 2.** Chemotherapy response distribution

| Chemotherapy response | N | Percentage (%) |
|---|---|---|
| Good response | 83 | 73.5 |
| Poor response | 30 | 26.5 |

**Distribution of the platelet lymphocyte ratio (PLR)**

The distribution of the PLR based on chemotherapy response showed the PLR value on good chemotherapy responses had an average value of 135.44 ± 39.17, while the PLR value on poor chemotherapy responses had an average value of 305.95 ± 127.33. The results of the study are presented in table 3.

**Table 3.** Platelet Lymphocyte Ratio (PLR) Distribution

| Chemotherapy response | N | Mean ± SD | Median (min-Max) |
|---|---|---|---|
| Good response | 83 | 135.44 ± 39.17 | 127.30 (17.24 – 260.62) |
| Poor response | 30 | 305.95 ± 127.33 | 297.15 (37.20 – 620.36) |

**Relationship of sociodemographic characteristics and chemotherapy response in locally advanced stage breast cancer patients**

The relationship between sociodemographic characteristics and chemotherapy response of patients with locally advanced breast cancer were analyzed using the chi square statistical test. It is found that there was no significant relationship between sociodemographic characteristics (age, age at menarche, age at first pregnancy, age at menopause, family history, contraception, parity and subtype) to chemotherapy response ($p > 0.05$).

**Platelet/Lymphocyte ratio (PLR) cut off point value based on chemotherapy response in locally advanced stage breast cancer patients**

The ROC analysis result of the PLR value based on the chemotherapy response in patients with locally advanced breast cancer obtains a cutoff point value of ≤ 206.83 with an Area under the ROC curve (AUC) value of 91.8%. The results of the analysis are presented in table 4.

**Table 4.** Table of platelet lymphocyte ratio (PLR) and chemotherapy response

| Platelet lymphocyte ratio (PLR) | Chemotherapy response | | Total N(%) | P value |
|---|---|---|---|---|
| | Good (N) | Poor (N) | | |
| PLR ≤ 206.83 | 81 | 4 | 85 | 0.000 |
| PLR > 206.83 | 2 | 26 | 28 | |
| Total | 83 | 30 | 113 | |

Based on the 2x2 table between the PLR value and the chemotherapy response, it is found that the diagnostic measures had a sensitivity value of 98%, specificity of 87%, Positive Predictive Value of 95%, Negative Predictive Value of 93%, accuracy value of 95% and AUC value of 91.8%. The results of the analysis are presented in table 5.

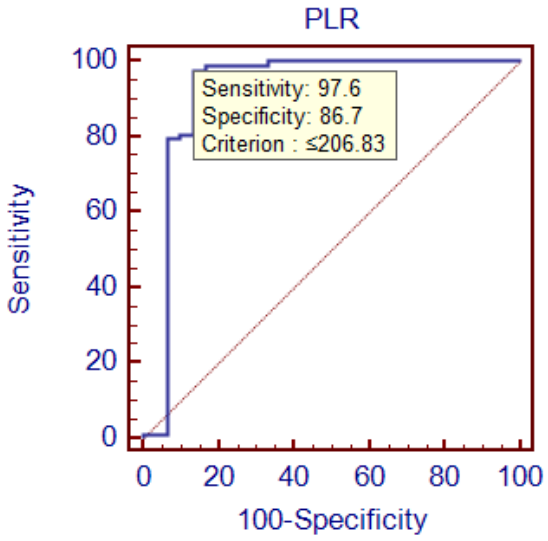


**Table 5.** *Platelet lymphocyte ratio (plr)* prognostic test on chemotherapy response in locally advanced stage breast cancer patients

| Diagnostic measures | Percentage value | 95% confidence interval |
|---|---|---|
| Sensitivity | 98 % | 91 – 100 |
| Specificity | 87 % | 68 – 96 |
| Positive predictive value | 95 % | 88 – 98 |
| Negative predictive value | 93 % | 75 – 99 |
| Accuracy | 95 % | 88 – 98 |
| Area under the ROC curve (AUC) | 91.8 % | 85.1 – 96.1 |
| Youden index J | 0.8426 % | |

**Relationship of platelet/lymphocyte ratio (plr) and chemotherapy response in locally advanced stage breast cancer patients**

The analysis of the relationship between PLR and chemotherapy response in patients with locally advanced breast cancer found that 95.3% cancer patients who had PLR ≤ 206.83 had a good chemotherapy response, compared to 7.1% cancer patients who had PLR > 206.83. The results of statistical tests using the chi square test found that there was a significant relationship between PLR and chemotherapy response in patients with locally advanced breast cancer (p value = 0.000) with an alpha value of 0.05 ($p < \alpha$).

## 4. Discussion

Platelets are small discoid non nucleated blood cells that are responsible in maintaining hemostasis. Platelets are about 2 µm in diameter and originate from the cytoplasm of megakaryocytes, the large bone marrow cells of the myeloid lineage. After they mature, they circulate in the human body for 7 to 10 days. If they are not used in a hemostatic reaction within this time, platelets will undergo apoptosis and are cleared through the liver and spleen.[11]

Platelets contain growth factors, such as platelet-derived growth factor (PDGF)[12,13,14], transforming growth factor (TGF) -β[15,16] and platelet-derived endothelial cell growth factor (PD-ECGF)[17,18,19]. These platelet-derived growth factors are often produced in large numbers by cancer cells

and contribute to metastasis, invasion, growth and cancer histology. A number of studies have also investigated the molecular mechanism of platelet-aggregating tumor cells known as tumor cell induced platelet aggregation (TCIPA).[20] Interactions between platelets and tumor cells are facilitated by major platelet receptors and ligands that mediate adhesion and aggregation. These include GPIb-IX-V and GPIIb / IIIa, interestingly, it has also been identified on several cancer cells surface such as breast cancer MCF7, B16 amelanotic melanoma, and 3LL Lewis lung carcinoma cells.[21,22] Peripheral platelet count is thus work as an indicator of tumor activity.

Lymphocytes are known to be responsible for the immune response to tumor growth. The number of peripheral lymphocytes is an indicator of tumor suppression. The mechanism by which the platelet/lymphocyte ratio and chemotherapy sensitivity are correlated is thought to occur due to the increase in myelosuppression and the decrease in platelet count with chemotherapy. Furthermore, chemotherapy increases the lymphocyte count by activating the immune response. It is thought to relatively decrease the platelet/lymphocyte ratio and increase the antitumor effect. This results in patients with low platelet/lymphocyte ratio, low platelet count and high lymphocyte count, exhibiting high antitumor activity, good prognosis and chemotherapy sensitivity. [8,9,23]

This study examined 113 patients with locally advanced breast cancer, in which 89 patients (78.8%) were above 40 years old with age range between 27-68 years old. Research conducted by Lopez et al, also stated that out of 288 locally advanced breast cancer patients, there were 239 patients (82.7%) of breast cancer patients aged above 40 years old, with an age range of 27-85 years old. [9]

Most of the breast cancer patients in this study had Luminal B subtype breast cancer (69%). This result is in line with the research conducted by Lopez et al that of 288 locally advanced breast cancer patients, the majority of breast cancer subtypes were the Luminal B subtype (47.6%).[9]

**Sociodemographic characteristics relationship to the chemotherapy response in locally advanced stage breast cancer patients**

The relationship of sociodemographic characteristics to the chemotherapy response of patients with locally advanced breast cancer were analyzed using the chi square statistical test. It is found that there was no significant relationship between sociodemographic characteristics (age, age at menarche, age at first pregnancy, age at menopause, family history of breast cancer, history of hormonal

contraception usage, history of childbirth and cancer subtype) to chemotherapy response (p> 0.05). These results are in line with research conducted by Lopez et al, who reported that there was no sociodemographic relationship with chemotherapy response.[9] This is also in line with the research of Zhang M et al, Zhu Y et al, Asano et al which stated that there was no relationship between clinical pathology characteristics and chemotherapy response[8,23,24]

**Platelet lymphocyte ratio (PLR) distribution**

The distribution of the PLR based on chemotherapy response shows the result of the PLR value analysis on good chemotherapy responses has an average value of 135.44 ± 39.17, while the PLR value on poor chemotherapy responses has an average value of 305.95 ± 127.33. These results are consistent with research conducted by Asano et al. Who reported in their study that patients with low PLR values (≤ 150) had a good chemotherapy response.

**Platelet/lymphocyte ratio (PLR) cut off point value based on chemotherapy response in locally advanced stage breast cancer patients**

The results of the ROC analysis of the PLR value based on the chemotherapy response of patients with locally advanced breast cancer obtained a cut off point value of ≤206.83 with an Area under the ROC curve (AUC) value of 91.8%. Based on the 2x2 table between the PLR value and the chemotherapy response, it was found that the diagnostic measures had sensitivity value of 98%, specificity of 87%, Positive Predictive Value 95%, Negative Predictive Value 93%, accuracy 95% and AUC 91.8%. These results conclude that PLR can be used as a predictor of neo-adjuvant chemotherapy response in breast cancer patients and has a good degree of accuracy.

**Relationship of platelet/lymphocyte ratio (PLR) and chemotherapy response in locally advanced stage breast cancer patients**

The analysis of the relationship between PLR and chemotherapy response in patients with locally advanced breast cancer found that 95.3% cancer patients who had PLR ≤ 206.83 had a good chemotherapy response, compared to 7.1% cancer patients who had PLR > 206.83. The results of statistical tests using the chi square test found that there was a significant relationship between PLR and chemotherapy response in patients with locally advanced breast cancer (p value = 0.000) with an alpha value of 0.05 ($p < \alpha$).

These results are in line with research conducted by Lopez et al, which reported that breast cancer patients with low PLR (<150) had a better chemotherapy response than breast cancer patients with high PLR (> 150).[9]

Research conducted by Asano et al, stated that a low PLR value had a high response to neo-adjuvant chemotherapy and had a correlation (p = 0.019) so that PLR can be used as a predictor of neo-adjuvant chemotherapy response.

Platelets are cells with many growth factors and the number of platelets can be an indicator of cancer cell activity. A low platelet count indicates low cancer cell activity. Chemotherapy itself triggers myelosuppression and decreases platelet count, and furthermore increases the lymphocyte count by activating the immune response.[8]

Research conducted by Zhu Y et al stated that high PLR is associated with poor overall survival (OS) and disease free survival (DFS) in breast cancer patients.[24] Zhu Y et al, also stated that PLR can be used as a reliable marker to assess the prognosis of breast cancer in patients undergoing chemotherapy.[24]

The systemic inflammatory response may facilitate tumor progression including initiation, progression and metastasis.[24,25] In addition, recent evidence suggests platelets may protect tumor cells from immune system elimination and are involved in the development of tumor aggressiveness.[26] Platelets can promote transendothelial tumor cell migration and metastasis through P2Y2 receptor mediation.[27] Platelets can secrete various growth factors including platelet derived growth factor (PDGF)[12,13,14], platelet activating factor (PAF)[28], and vascular endothelium growth factor (VEGF)[29], which in turn can support tumor growth, angiogenesis and metastasis.[32] Therefore, an increase in platelet count has a negative effect on patient survival.[30] On the other hand, lymphocytes have an important role in the tumor's inflammatory response.[31] Lymphocytes have anti-tumor activity by inducing cytotoxic cell death and inhibits tumor proliferation.[32] Several studies have reported that the increase of lymphocyte infiltration into tumor tissue resulted in better survival outcomes in cancer patients.[33,34]

## 5. References


1. Manuaba TW. Kanker Payudara dalam Panduan Penatalaksanaan Kanker Solid PERABOI. Jakarta: Sagung Seto. 2010
2. Suyatno, Pasaribu ET. Bedah Onkologi : Diagnosis dan Terapi. Jakarta: CV Sagung Seto; 2010.
3. Komite Penanggulangan Kanker Nasional. Panduan Penatalaksanaan Kanker Payudara. Kementerian Kesehatan RI. 2015
4. *International Agency for Research on Cancer (IARC) / WHO.* (2018). GLOBOCAN 2018: Breast. Diakses melalui http://gco.iarc.fr/today/fact-sheets-cancers pada tanggal 20 September 2019.
5. Youlden, D. R., Cramb, S. M., Yip, C. H., dan Baade, P. D. Incidence and mortality of female breast cancer in the Asia-Pacific region. Cancer Biol Med. 2014; 11 (2): 101-115
6. Purwanto H. Kanker Payudara Lanjut Lokal dan Kemoterapi Neoadjuvan sebagai Upaya Peningkatan Respon. Medicinus. 2011.Vol 24;4-8.
7. Purwanto H, Handojo D, Haryono SJ, Harahap WA, editor. Terapi Dalam: Panduan Penatalaksanaan Kanker Payudara. Jakarta: Perhimpunan Ahli Bedah Onkologi Indonesia; 2015.
8. Asano Y, Kashiwagi S, Onoda N, Noda S et al. Platelet lymphocyte ratio as a useful predictor of the therapeutic effect of neo-adjuvant chemotherapy in breast cancer. PLOS One. 2016.
9. Lopez JC, Zapata AF, Agudelo LL, Trespalacios EV. Platelet to lymphocyte ratio as a predictive factor of complete pathologic response to neo-adjuvant chemotherapy in breast cancer. PLOS One. 2018.
10. Xu J, Ni C, Ma C et al. Association of neutrophil/lymphocyte ratio and platelet/lymphocyte ratio with ER and PR in breast cancer patients and their changes after neo-adjuvant chemotherapy. Clin Transl Oncol. 2017.
11. Yan M, Jurasz P. The role of platelets in the tumor microenvironment: from solid tumors to leukemia. Biochimica et Biophysica Acta. 2015.

12. Ariad S, Seymour L, Bezwoda WR. Platelet derived growth factor (PDGF) in plasma of breast cancer patients: correlation with stage and rate of progression. Breast Cancer Res Treat. 1991; 20:11-17.

13. Heldin CH, Westermark B, Wasteson A. Platelet derived growth factor: purification and partial characterization. Proc Natl Acad Sci USA. 1979.

14. Betsholtz C, Johnsson A, Heldin CH, et al. cDNA sequence and chromosomal localization of human platelet derived growth factor A-chain and its expression in tumour cell lines. Nature. 1986.Miyazono K, Yuki K, Takaku F, et al. Latent forms of TGF-beta: structure and biology. Ann N Y Acad Sci. 1990; 593:51-8

15. Sporn MB, Roberts AB. Transforming growth factor-beta. Multiple actions and potential clinical applications. JAMA. 1989; 262(7): 938-41

16. Miyazono K, Okabe T, Urabe A, et al. Purification and properties of an endothelial cell growth factor from human platelets. J Biol Chem. 1987.

17. Ishikawa F, Miyazono K, Hellman U, et al. Identification of angiogenic activity and the cloning and expression of platelet derived endothelial cell growth factor. Nature. 1989.

18. Heldin NE, Usuki K, Bergh J, et al. Differential expression of platelet derived endothelial cell growth factor/thymidine phosporylase in human lung carcinoma cell lines. Br J Cancer. 1993.

19. Jurasz P, Alonso-Escolano D, Radomski MW. Platelet cancer interactions: mechanisms and pharmacology of tumour cell-induced platelet aggregation. Br. J. Pharmacol. 2004.

20. Alonso-Escolano D, Strongin AY, Chung AW et al. Membrane type 1 matrix metalloproteinase stimulates tumour cell induced platelet aggregation. Br. J. Pharmacol. 2004

21. Honn KV, Timar J, Onada JM et al. Alpha Iib beta 3 integrin expression and function in subpopulations of murine tumors. Exp. Cell Res. 1992.

22. Zhang M, Huang X, Song Y, Gao P et al. High platelet to lymphocyte ratio predicts poor prognosis and clinicopathological characteristicss in patient with breast cancer: a meta analysis. Biomed Research International. 2017.

23. Zhu Y, Si W, Sun Q, Qin B et al. Platelet lymphocyte ratio acts an indicator of poor prognosis in patients with breast cancer. Oncotarget. 2017; 8(1): 1023-1030.

24. Coussen LM, Werb Z. Inflammation and cancer. Nature. 2002;420:860-867.

25. Gay LJ, Felding Habermann B. Contribution of platelets to tumour metastasis. Nat Rev Cancer. 2011; 11:123-134.

26. Schumacher D, Strilic B, Sivaraj KK, Wettschureck N, Offermanns S. Platelet derived nucleotides promote tumor cell transendothelial migration and metastasis via P2Y2 receptor. Cancer Cell. 2013; 24:130-137.

27. Van den Bosch H, de Vet EC, Zomer AW. The role of peroxisomes in ether lipid synthesis. Back to the roots of PAF. Adv Exp Med Biol. 1996; 416:33-40.

28. Sullivan LA, Brekken RA. The VEGF family in cancer and antibody based strategies for their inhibition. Mabs. 2010;2:165-175.

29. Goubran HA, Burnouf T, Radosevic M, El-Ekiaby M. The platelet-cancer loop. Eur J Intern Med. 2013; 24: 393-400.

30. Smyth MJ, Dunn GP, Schreiber RD. Cancer immunosurveillance and immunoediting: the roles of immunity in supressing tumor development and shaping tumor immunogenicity. Adv Immunol. 2006; 90:1-50.

31. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer related inflammation. Nature. 2008; 454:436-444.

32. Nguyen N, Bellile E, Thomas D, et al. Tumor infiltrating lymphocytes and survival in patients with head and neck squamous cell carcinoma. Head Neck. 2016; 38:1074-1084.

33. Mao Y, Qu Q, Chen XS, et al. The prognostic value of tumor infiltrating lymphocytes in breast cancer: a systematic review and meta analysis. Plos One. 2016; 11-13.